NEW CONCEPTS OF CARDIOGENIC SHOCK: PRESERVATION OF ISCHEMIC MYOCARDIUM*

STEPHEN SCHEIDT, M.D., DANIEL R. ALONSO, M.D., GARY WILNER, M.D., AND THOMAS KILLIP, M.D.

Department of Medicine
New York Hospital-Cornell Medical Center
New York, N.Y.

CARDIOGENIC shock occurs in 10 to 15% of hospitalized patients who have acute infarction. In most institutions the mortality exceeds 85%.[1] Most deaths in patients hospitalized with acute infarction result from shock or "pump failure." There is little evidence that improvements in the therapy of acute myocardial infarction have significantly lowered the mortality from shock.

It is now reasonably certain that massive myocardial damage is present in most patients with cardiogenic shock when remediable causes such as hypovolemia or sepsis are excluded.

In a group of patients studied by Dr. Daniel Alonso of The New York Hospital-Cornell Medical Center, total damage to the left ventricle averaged 51.2% (range: 34.8 to 68.3%) in 22 patients with cardiogenic shock and 22.9% (range: 14.5 to 30.7%) in 10 patients who died suddenly after acute myocardial infarction ($p<.01$).[2] There was no significant difference in the mass of old (more than two months) or intermediate (three weeks to two months) damage; the highly significant difference in total infarction between the two groups was explained by the larger mass of recent infarction in the shock patients (31.3%) as compared with the sudden-death group (12.1%, $p<.01$). Thus, patients who succumb from cardiogenic shock have larger fresh infarcts and less functioning myocardium than those who do not develop shock (Figure 1). Our data are in agreement with those of other workers who

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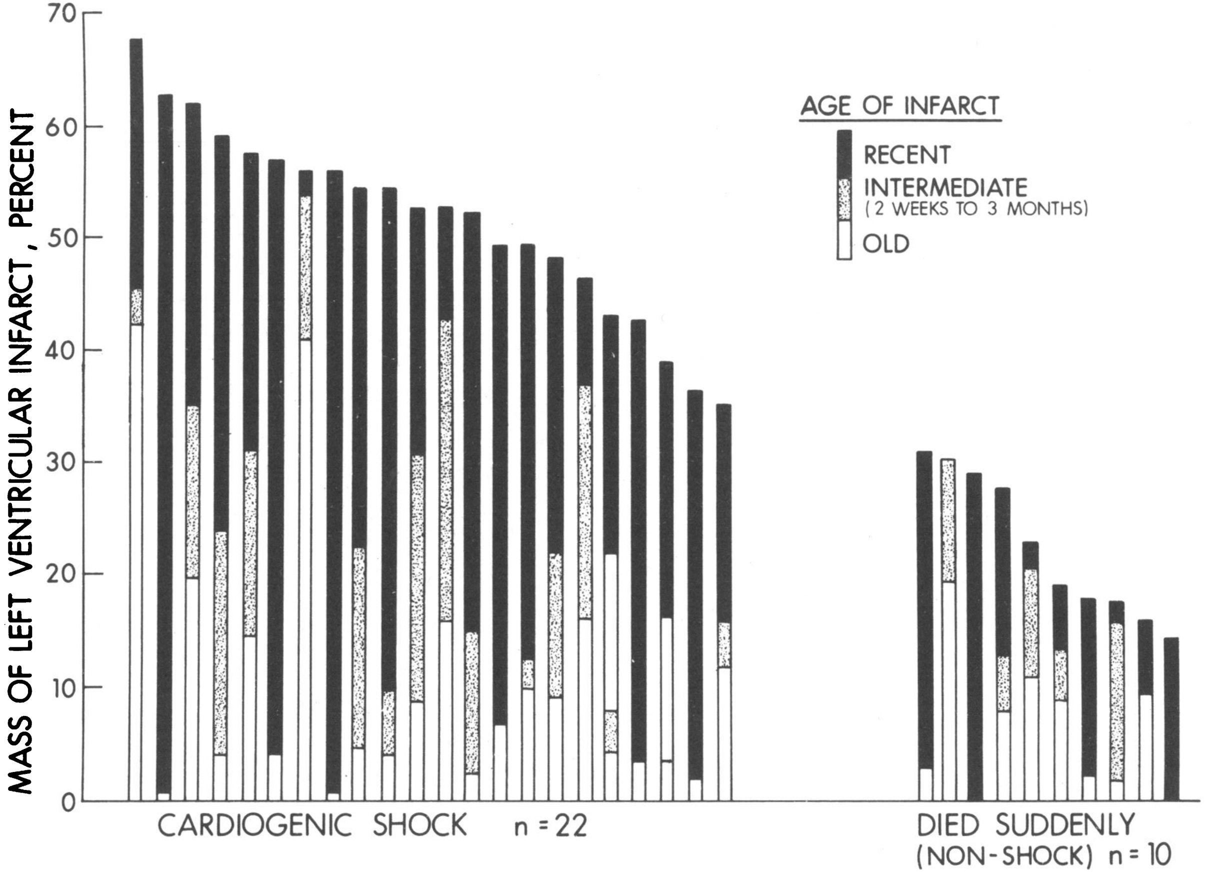

Fig. 1. Mass of left-ventricular infarction in 22 individuals with cardiogenic shock and 10 control patients with acute myocardial infarction who died suddenly in the hospital. The appearance of shock is best correlated with the amount of total damage. Reproduced by permission from The American Heart Association, Inc., and Alonso, D. R., Scheidt, S., Post, M., and Killip, T.: Pathophysiology of cardiogenic shock: Quantification of myocardial necrosis, clinical, pathologic and electrocardiographic correlation. *Circulation 48*:588-96, 1973.

measured myocardial damage in shock by slightly different techniques.[3, 4]

Of great importance is the fact that myocardial damage may not occur as a single catastrophic event. In our 22 patients with shock, extension of the original infarct was seen in 18 patients and multiple noncontiguous recent infarcts of varying age were seen in seven patients. Extension or multiple recent infarction often occurred in close temporal proximity to the clinical onset of shock (Figure 2). Although extension of infarction was common, it was not often recognized clinically. Only two of the 18 extensions were associated with clinical evidence of further infarction and only three patients had electrocardiographic changes suggesting extension. These observations suggest that the extensive loss of myocardium incriminated in the genesis of shock occurs in a stepwise but often unrecognized fashion.

In a study of 73 patients with shock and 474 patients with acute myocardial infarction without shock seen at The New York Hospital-Cornell Medical Center over a five-year period, we found that a variety of clinical factors were less important than the occurrence of massive myocardial damage in predisposing to shock.[1] Age distribution, the incidence of prior angina, myocardial infarction and congestive heart failure, and delay from the onset of symptoms to hospitalization were similar in shock and nonshock patients. Many patients had no obvious precipitating factor other than myocardial infarction itself preceding shock. Most cardiac arrhythmias were secondary and the result of shock, rather than primary and the cause of shock; more than two thirds of the patients with shock had sinus rhythm at the onset of shock.

Thus, if cardiogenic shock is usually the result of massive myocardial necrosis and this damage often occurs in a stepwise or progressive fashion over a period of hours or days, it is possible that appropriate early intervention may limit myocardial damage and prevent shock. Favorable effects of treatment would presumably be based on preservation of tissue in the marginal ischemic zone that surrounds a myocardial infarct[5] and on preventing extension of the infarct.

That the extent of myocardial necrosis can be affected by manipulation of various physiologic factors has been demonstrated in experimental animals by several investigators. Maroko et al. increased or decreased the size of experimental myocardial infarcts of reproducible size created by coronary artery occlusion at a fixed anatomic site in dogs

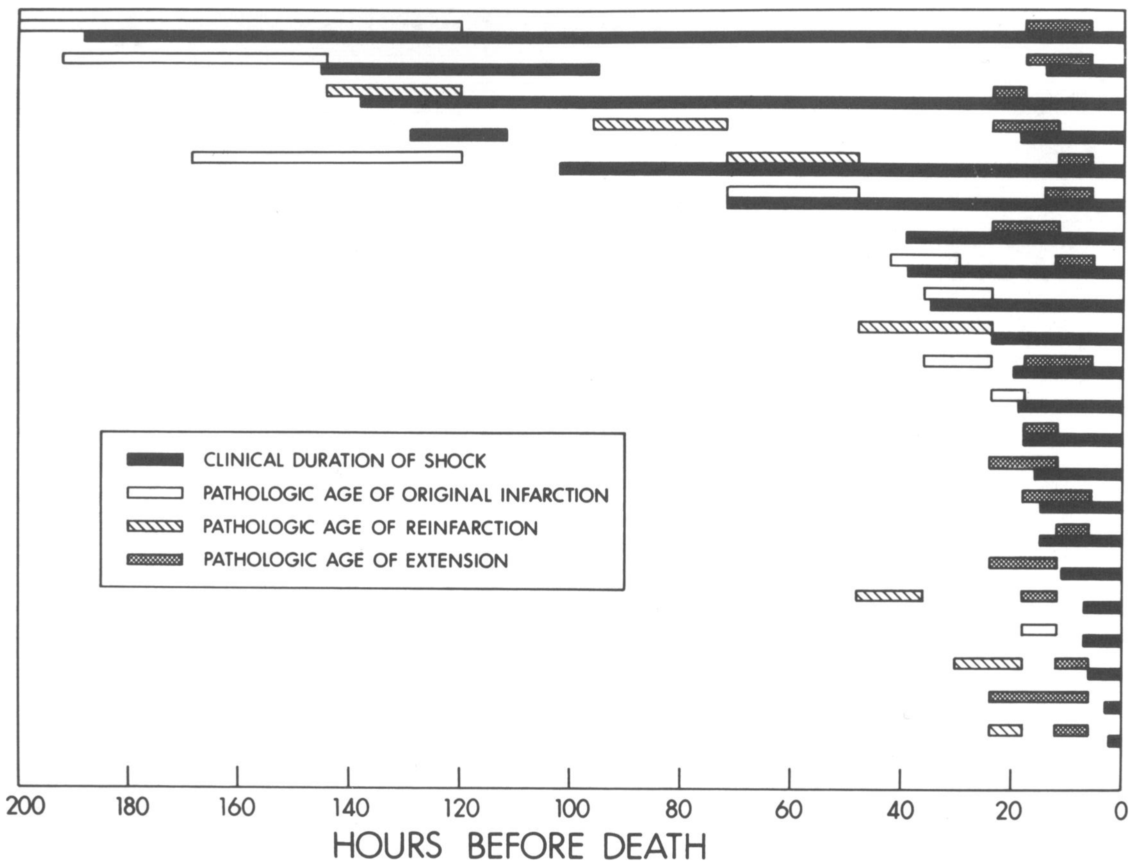

Fig. 2. Chronologic relations between clinical and pathologic events in 22 patients dying from cardiogenic shock. The age of infarction, extension, or reinfarction was estimated by standard pathologic techniques and is shown as a range of minimum to maximum estimated age. Original infarcts have been omitted when they occurred long before the clinical onset of shock. Reproduced by permission from The American Heart Association, Inc., and Alonso, D. R., Scheidt, S., Post, M., and Killip, T.: Pathophysiology of cardiogenic shock: Quantification of myocardial necrosis, clinical, pathologic and electrocardiographic correlation. *Circulation 48*:588-96, 1973.

PRESERVATION OF ISCHEMIC MYOCARDIUM

Reduce myocardial oxygen demand
Decrease afterload (nitroprusside, trimethaphan, phentolamine, nitroglycerine, counterpulsation)
Decrease contractility (propranolol)
Decrease heart size (digitalis, diuretics)
Decrease stroke volume (mechanical left-ventricular bypass)
Decrease peripheral demand (hypothermia)
Increase myocardial oxygen supply
Increase coronary flow (surgical revascularization, increased perfusion pressure, coronary vasodilators, counterpulsation)
Increase blood oxygen content (hyperbaric oxygen, hemoglobin substitutes)
Increase oxygen delivery (shift hemoglobin dissociation curve)
Provide new substrates (high concentration glucose, glucose-insulin-potassium, free fatty acids, Krebs cycle intermediates)
Alter metabolic pathways (increase anaerobic glycolysis, increase myocardial glycogen stores, alter rate-limiting enzymes)
Miscellaneous
Protect cellular structure (hyperosmolar agents)
Protect endothelium; prevent platelet aggregation (aspirin, dipyridamole, propranolol, indomethacin, adenosine, prostaglandins)
Preserve lysosomes (corticosteroids, anti-inflammatory agents, antimalarial agents, chlorpromazine)

with the use of various drugs and other maneuvers.[6] Although the results of Maroko's experiments may not apply directly to clinical situations, it was nevertheless shown that the final extent of infarction may be influenced by physiologic and pharmacologic factors in addition to the anatomic coronary lesion. Potential methods for limiting myocardial ischemia are summarized in the accompanying table.

Reduction of Myocardial Oxygen Demand

The determinants of myocardial oxygen demand include wall tension (in turn related to systolic intraventricular pressure, ventricular size, and geometry), systolic ejection time, heart rate, stroke volume, and contractility. Therapeutic reduction of the heart's need for oxygen when the supply is reduced by coronary stenosis or thrombosis might restore the metabolic balance.

In studies by Cohn and his co-workers, reduction of aortic impedance, or "afterload," with the peripheral vasodilator nitroprusside were found to result in increased cardiac output and decreased left-ventricular end-diastolic pressure in patients with acute myocardial infarction[7] and chronic congestive heart failure.[8] Shell et al. suggested that trimethaphan, another peripheral vasodilator, decreased the extent of myocardial infarction as compared to pretreatment predictions.[9] In the above studies, apparently favorable hemodynamic effects were achieved without much fall in aortic systolic pressure. Phenotolamine has been reported to produce similar hemodynamic effects.[10] The effects of nitroglycerine, which has multiple pharmacologic actions, including reduction of afterload as well as preload, are variable and require further study in trials conducted after acute myocardial infarction.[11, 12] Reduction of afterload alone may not be feasible in patients with hypotension and borderline coronary perfusion. Indeed, it may be dangerous under such circumstances if coronary perfusion in stenotic vessels were compromised.

Afterload is also decreased during counterpulsation, a technique in which volume is removed from the aortic root just before ventricular systole, thus reducing impedance to ejection, and returned during ventricular diastole (when the aortic valve is closed and the ventricle unaffected by aortic events).[13] Favorable clinical, hemodynamic, and metabolic effects of intra-aortic counterpulsation in animals and in patients with cardiogenic shock have been reported by several investigators.[13-15]

Reduction of contractility–with propranolol, for example–should decrease myocardial oxygen consumption, providing ventricular diameter and thus wall tension are not much increased. Maroko et al. found that the extent of myocardial ischemia in dogs was decreased after the administration of propranolol before and up to several hours after experimental coronary occlusion.[16] Mueller et al. demonstrated favorable effects on myocardial metabolism in 20 patients with acute myocardial infarction who received propranolol within a few hours of infarction.[17, 18] Although propranolol may be useful in patients without congestive heart failure, its administration in the presence of congestive failure or shock may be deleterious if myocardial function is further compromised.

Digitalis, which increases myocardial contractility and myocardial oxygen consumption in the normal heart, has been shown to increase the extent of myocardial ischemia in normal dogs with experimental coronary occlusion.[6] However, in the failing heart, the net effect of digitalis is reduction in heart size and slowing of the rate with a consequent decrease in wall tension and decreased myocardial oxygen consumption. Indeed, Watanabe found a decreased area of myocardial ischemia after experimental coronary occlusion with use of ouabain in the failing canine heart.[19]

Since myocardial oxygen consumption is positively correlated with heart rate, bradycardia should reduce myocardial demand. Redwood et al. were able to limit myocardial ischemia in the dog when bradycardia was induced by vagal stimulation.[20]

Finally, various mechanical devices for left-ventricular bypass and temporary circulatory support have been employed experimentally, but little or no systematic information is available on the long-term efficacy of such circulatory assistance. The techniques invariably require surgical manipulation in the acutely ill patient. Since shortening of the contractile element (which is proportional to stroke volume) accounts for only a small proportion of total myocardial oxygen need,[21] even the major reductions in stroke volume achievable with mechanical circulatory assistance may not have much effect in reducing the consumption of oxygen by the myocardium.

Increase in Myocardial Oxygen Supply

Surgical revascularization, successful in many patients with chronic ischemic heart disease and angina pectoris, has been suggested as a possible mode of minimizing myocardial damage after acute myocardial infarction.[22-26] Several patients with cardiogenic shock have also been treated surgically.[22, 23, 27] There is a disturbing initial report that reperfusion after experimental myocardial infarction sometimes produced hemorrhagic infarcts that were larger than predicted before restoration of coronary flow to the area,[28] although the same authors eventually concluded that early reperfusion had favorable early[29] and late[30] effects on local myocardial function and on the histologically determined area of infarction. The risks of surgical operations performed during the acute phase of myocardial infarction are almost certainly greater than the risks encountered in elective operations and may be prohibitive.

It may be possible to increase coronary flow by raising coronary perfusion pressure, although it is not known whether flow to areas served by severely stenotic or occluded coronary vessels can be affected by increasing aortic diastolic pressure alone. L-norepinephrine, although it increases both cardiac contractility and, presumably, myocardial oxygen needs, improves myocardial metabolism when administered in modest doses, possibly because of increased coronary perfusion pressure resulting from the increased aortic pressure.[14] Phenylephrine has been shown to decrease the extent of myocardial ischemia in experimental coronary occlusion.[6]

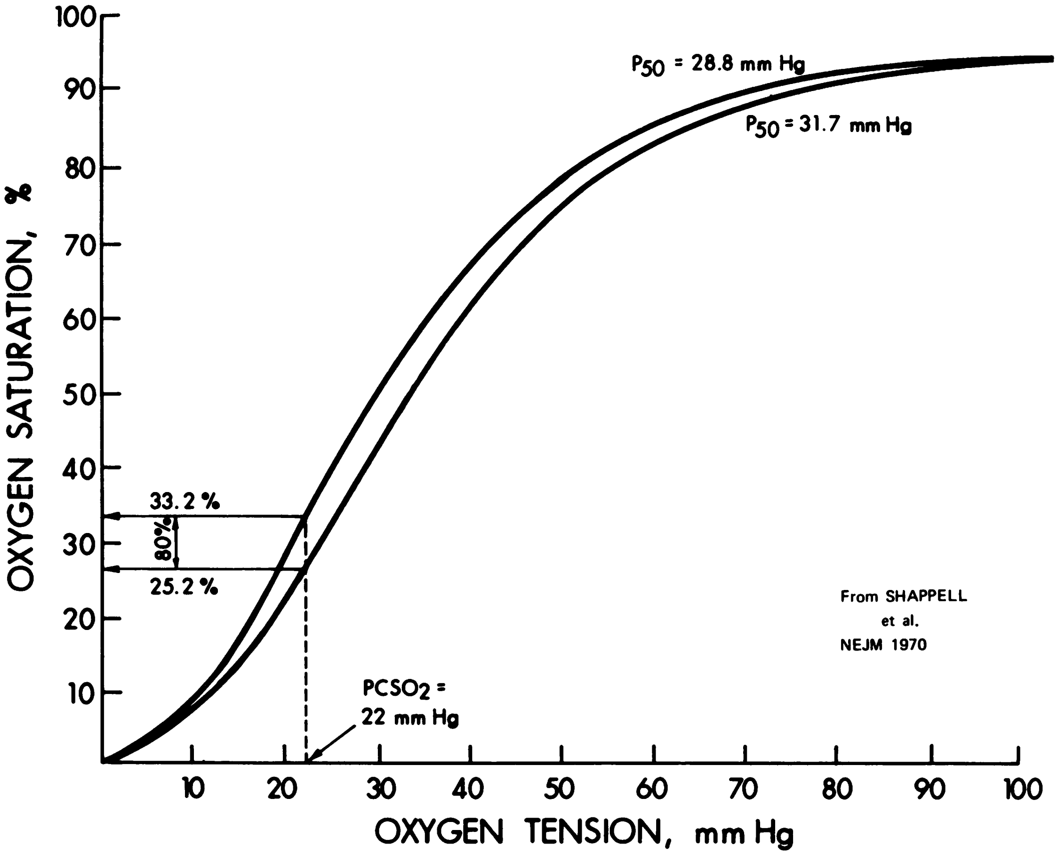

Fig. 3. Two hemoglobin dissociation curves, with P_{50} of 28.8 and 31.7 mm. Hg, respectively. At $pO_2 = 22$, the oxygen tension of the coronary sinus, a rightward shift of the dissociation curve as shown results in the unloading of 8% more oxygen to the myocardium. Adapted from Shappell, S. D., Murray, J. A., Masser, M. G., Wills, R. E., Torrance, J. D., and Lenfant, C. J. M.: Acute change in hemoglobin affinity for oxygen during angina pectoris. *New Eng. J. Med. 282*:1219, 1970.

Counterpulsation, by returning volume to the aortic root in diastole, increases diastolic pressure. The favorable metabolic and clinical effects of intra-aortic balloon pumping mentioned above may be in part related to this hemodynamic effect. External counterpulsation by synchronized diastolic compression of the lower extremities is a noninvasive technique that may be applicable to patients who are less severely ill. Clinical benefit in the treatment of cardiogenic shock has been suggested, but hemodynamic or metabolic documentation remains meager.[31-34]

Additional oxygen might be made available to an ischemic myocardium by increasing the concentration of oxygen in the blood or its availability to the tissues. Although the almost total saturation of hemoglobin at ambient oxygen tension precludes any large increase in blood oxygen content in normal patients by increasing the concentration of inspired oxygen, small increases in inspired oxygen exert demonstrable effect in patients with ischemic heart disease. Arterial oxygen tension is significantly reduced in many patients with acute myocardial infarction.[35] Increased concentrations of inspired oxygen improve arterial oxygen saturation somewhat, but often not to normal levels, probably because of pulmonary arteriovenous shunting.[36]

Hyperbaric oxygen, which could add substantial amounts of dissolved oxygen to blood, is an attractive theoretical method of treatment. For example, at two atmospheres pressure of pure oxygen an 18% increment of normal oxygen content can be dissolved in the blood. Preliminary and usually uncontrolled reports of treatment of small groups of patients with hyperbaric oxygen are available.[37] The technique, however, is expensive, and presents such grave technical and nursing problems that it is unlikely to achieve widespread use in the treatment of acute myocardial infarction. Hemoglobin substitutes are under development and the future possibility of increasing blood oxygen capacity with such artificial substances cannot be discounted.

Oxygen delivery to tissues might be increased by altering the binding of oxygen by hemoglobin. An increase in P_{50} (the partial pressure of oxygen at 50% saturation of hemoglobin, a single measurement that serves to describe a curve with certain hemoglobin-oxygen affinity) from the normal of 26 mm. Hg to 30 mm. Hg increases myocardial unloading of oxygen (at the pO_2 of the coronary sinus) by 8% (Figure 3). Such a small increase in P_{50} occurs in patients with severe anemia, low-output heart failure, and cyanotic congenital heart disease among other conditions, and has been induced artifically by overnight incubation of primate blood with inosine, phosphate, and pyruvate,[38] or by administration of propranolol.[39] Whether these manipulations might have clinical usefulness remains to be determined.

An increased production of energy, even without increased myocardial oxygen supply, might be achieved by altering the metabolic pathways. Increases in anaerobic glycolysis can be achieved by the addition of various substrates other than glucose, including palmitate[40] and other tricarboxylic acid cycle metabolites. Promotion of glycogen formation, induction of concentration changes in rate-limiting enzymes, or provision of new substrates like amino acids or free fatty acids may be other ways of improving the production of energy, even in the absence of a sufficient supply of oxygen.

There has been a resurgence of interest in the use of glucose-insulin-potassium. This was first suggested by Sodi-Pallares in the early 1960s,[41] but early clinical reports were contradictory in their evaluation of its effectiveness.[42-44] The end-points used in earlier evaluation, such as mortality, occurrence of arrhythmia, or evolution of electrocardiographic changes, may not have been optimal, and differences in amounts administered, duration of therapy, and method and route of administration further cloud the issue.[42] Careful reevaluation using more precise methodology for measurement of the extent of myocardial ischemia is needed. Maroko et al. found a decrease in the apparent extent of ischemia after experimental coronary artery occlusion in dogs treated with glucose-insulin-potassium.[45] With this combination of agents, Nocero et al. were able to show benefit in increasing the pacing-induced angina threshold in patients with ischemic heart disease but not acute myocardial infarction,[46] while Lesch and his co-workers could not.[47] The mechanism of action of glucose-insulin-potassium is unknown; it is conceivable that the observed effects, if any, are not due to metabolic changes at all. The solution generally employed has high osmolarity, and this may explain certain observations (*vide infra*).

Finally, various other interventions have been suggested for the limitation or reduction of myocardial ischemia or necrosis. Prevention of cellular or endothelial swelling with hyperosmolar solutions is under study. The former may have beneficial effects by preventing the dispersion of enzyme systems or damage to cellular organelles, while the latter might improve small vessel blood flow. Beneficial effects of infusions of mannitol, which apparently increased total collateral coronary flow and contractility while at the same time decreasing the area of electrocardiographic ischemia, have been reported in canine heart preparations.[48] Hyaluronidase has been reported to reduce the extent of myocardial ischemia in experimental coronary artery occlusion in dogs[49] as well as in man.[50] The mechanism is unknown. Corticosteroids have a similar effect in the dog.[51] Various theories, including stabilization of the lysosomal membrane, have been invoked in explanation for an apparently favorable effect, as yet without convincing documentation.

It has been suggested that myocardial ischemia may be reduced by protecting the vascular endothelium, and agents affecting platelet aggregation are likely drugs for trial. Haft has shown a reduction in the extent of epinephrine-induced myocardial necrosis after aspirin or dipyramidole pretreatment in dogs. He attributed the protective effect of these agents to their antiplatelet ADP actions.[52] Various drugs known to prevent the aggregation of platelets might be tried for their effect in limiting myocardial ischemia.

The application of appropriate therapy to limit myocardial ischemia may well differ in different patients. For example, those who have diastolic hypertension might benefit from nitroprusside or trimethaphan, while in those with undue anxiety and tachycardia but not heart failure propranolol might be preferable. Critical evaluation of the various therapeutic interventions in patients with ischemic heart disease, as well as in experimental models, is urgently needed. Development of methods for better quantification of ischemia or necrosis will be vital, since the end result of successful new forms of therapy will be a significant reduction in the size of the myocardial infarct and the prevention of extention. Careful clinical observation and critical experimental analysis are required. Testimony, faith that a particular treatment is effective, and uncontrolled studies will not be acceptable as contributions to medical progress.

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